Remarks

Claims 11, 15, 21-24, 26-30, and 32-35 are pending and examined in this application. Claim 11, 15 and 3 are amended to more particularly point out and distinctly claim the invention. The claims stand rejected from the Final Office Action of April 21, 2005. Applicants respectfully request reconsideration and withdrawal of the current rejections based on the amendments and the following remarks.

Rejections under 35 U.S.C. 112, first paragraph

Claims 11, 15, 21-24, 26-30, and 32-35 stand rejected under 35 U.S.C. 112, first paragraph for failing to comply with the enablement requirement. Withdrawal of these rejections are respectfully requested for the following reasons, which address the concerns raised in the April 21, 2005 Office Action and the March 16, 2005 interview.

A concern raised by Examiners Kaushal and Fredman in the March 16, 2005 interview as well as the April 21, 2005 Office Action relates to the definition of "pDC2 cells" in the claims. The claims are amended herewith to make clear that "pDC2 cells" are $CD4^+$, $CD3^-$ and $CD11c^-$.

Another concern raised by Examiners Kaushal and Fredman in the March 16, 2005 interview as well as in the enablement rejection in the April 21, 2005 Final Office Action is that the negative correlation between pDC2 levels and AIDS progression established in the instant application is simply due to the known reduction in interferon levels by pDC2 cells with age, as established by Shodell and Siegal, 2002, Scan. J. Immunol. 56:518-521 ("Shodell and Siegal, 2002")(reference already of record). This concern was particularly raised with the correlations on Table 1, on page 40 of the application.

Applicants first note that the study that is the basis for Table 1 took place over a three year period (Specification on page 32, line 31). Since reduction in interferon levels in pDC2 cells occurs over decades (Shodell and Siegal, 2002, Table 1 on page 519), the reduction in interferon levels would not be evident in the relatively short three year time frame in the study leading to the specification's Table 1.

The various correlation determinations in Table 1 also control for any effect due to aging. For example, the last listed correlation, "All symptomatic subjects who were suppressed" shows the same negative correlation between interferon levels (approximating pDC2 levels) and viral burden. If pDC2 levels did not correlate with viral suppression but only with aging, then there would be a positive correlation here (while still showing a negative correlation with $CD4^+$ counts) because this correlation measures the difference between interferon levels in individuals that had symptoms and later showed viral suppression. Since the viral suppression was at a later time point, the interferon levels would be expected to be lower at the later time point if those changes were due to aging and not viral load. Thus, a positive correlation would be expected in that analysis if the variation in apparent pDC2 levels were only due to age of the patient and not viral load. However, a negative correlation, similar to $CD4^+$ levels, was found.

Applicants also point to Table 2, which shows that suppression of HIV viremia positively correlates with reconstitution of interferon generation. If interferon production by pDC2 cells was only negatively influenced by age and not related to HIV viremia, the correlations in Table 2 would be negative, because that table measures changes in interferon levels after viral suppression. Since the correlations are positive in Table 2, pDC2 and interferon levels go up over time and not down. Thus, aging cannot be the cause of the positive correlation because a negative correlation would be expected if aging and not viral suppression were affecting the measured interferon levels.

It is also noted that Table 1 and Table 2 of the instant specification show a strong correlation between interferon generation and $CD4^+$ T cell counts for each condition analyzed. As shown by Shodel and Siegal, 2002, $CD4^+$ T cell levels do not go down with age, but are known to be strongly correlated with HIV viremia. If pDC2/interferon generation in those studies were influenced by age and not viremia, there would not be similar regression slopes for interferon generation and $CD4^+$ T cell counts.

The similar recovery of $CD4^+$ T cells and interferon generation with therapeutic suppression of HIV was also noted by Siegal et al., 2001, AIDS 15:1603-1612 (provided with the Amendment and Reply Under 37 C.F.R. 1.111 dated May 17, 2004 in this case).

Again, if interferon levels only negatively correlated with aging and not with HIV viremia levels, the interferon levels would go down with suppression of viremia, and would not show a rise with suppression of viremia as with $CD4^+$ cells.

Based on the above discussion, the reduction in interferon/pDC2 levels with increases in viremia discussed in the instant specification cannot be due to aging, since interferon levels went up or down with $CD4^+$ levels and not with age.

The confirmation of the negative correlation between pDC2 and HIV progression and positive correlation with the effectiveness of HIV treatment confirmed in Siegal et al., 2001, AIDS 15:1603-1612, and Feldman et al., 2001, Clin. Immunol. 101:201-210, as discussed in the Amendment and Reply dated May 17, 2004, further confirms the enablement of the claimed methods.

With regard to the concern that control values are not provided, applicants again assert that it would take only routine experimentation to establish controls for any individual. Such reference ranges could be established simply by drawing blood from the appropriate population and counting pDC2 cells using, e.g., the cell sorting methods established in the instant specification. Such a determination would not be considered undue experimentation, since there is no uncertainty in the methods used to make those determinations.

In light of the above discussion, Applicants respectfully request withdrawal of the enablement rejections under 35 U.S.C. 112, first paragraph.

Conclusion

Based on the claim amendments and the above discussion, Applicants respectfully request withdrawal of all rejections and passage of the claims to allowance. If there are any minor matters that prevent allowance of the claims, the PTO may contact the undersigned attorney to resolve those matters.

It is believed that no fee is required with this Reply and Amendment. If there are any unanticipated fees required to maintain pendency of this application, those fees can be withdrawn from Deposit Account No. 01-1785.

Respectfully submitted

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